Remarks

The present invention is directed to the discovery that an effective and safe immune response against *Campylobacter* can be raised in birds, in ovo, by administration of live Campylobacter cells as immunogen. It has also been surprisingly discovered that such vaccination is safe, and does not harm the developing bird. Applicant respectfully believes that this invention is neither present in the prior art, nor is it suggested by any combination of teachings found in the prior art.

Support for the present amendment to Claim 1 "wherein said live cells are free of neutralizing antibodies or neutralizing antibody fragments" appears clearly at Page 3, lines 37-39 in Applicant's underlying PCT/IB2004/003806 specification.

The section 102 rejection over Thoma et al.

In the general practice of the avian vaccination art, it is generally recognized that direct vaccination into an egg with live bacteria is harmful to the developing embryo and may cause significant mortality. For example, live *Salmonella* and *E.coli* administered into a live egg are known to cause morbidity and mortality. The vaccinating microorganisms may end up in various tissues of the egg, and being opportunistic, may trigger infections against which the developing embryo is not able to properly – and quickly –defend against. This is hardly surprising, since even though such vaccines may present the host animal with an overall excellent array of immunizing antigens, the pathogen is nonetheless live. Obviously, direct injection of live pathogens into the blood of mammals is similarly not recommended.

Although the Examiner has cited *Thoma et al.* (US 6,440,408) as anticipatory, in fact this reference sets the stage for the present invention. According to the clear teachings of this reference, live bacterial vaccines are unsafe, and should not be administered to eggs. Therefore, according to the teachings of the Thoma et al. invention (see claim 18 thereof, and all throughout that specification), the vaccine consists of live bacterial cells which are invariably conjugated to neutralizing factors such as neutralizing antibodies and neutralizing antibody fragments. Administration of live bacterial cells without such neutralizing factors is not disclosed in the '408 patent, and the entire thrust of the specification is to teach fully away from the practicality and operability of the present invention. Finally, although the'408 specification contains numerous working examples, none are actually directed to *Campylobacter*. That the use of live, non-neutralized pathogens as antigen is NOT

contemplated by Thoma et al. is clearly evident all throughout column 2 of the granted patent, see for example, lines 31-35, lines 48-50, and most particularly at lines 62-64 which recites "Use of the present vaccine conjugates are [sic] safer than the use of the unconjugated organism…….

Should the Examiner take the view that the "live cells" as mentioned in presently pending claim 1 are grammatically permitted to "comprise" an additional antibody components, i.e. that a live bacterium-antibody conjugate is nonetheless still a live bacterium, then Applicant's response is as follows. Irrespective of whether the live cells can generally comprise other components according to the meaning of the present invention, the compositions recited in the '408 patent are a *completely different invention*, as the invention of the '408 patent was clearly deemed by those authors to be essentially inoperable, in a practical sense, without added antibody.

However, it is believed that the rejection has been additionally addressed by the amendment of Claim 1 herewith to clearly recite that the use of neutralizing antibody or antibody fragment complexes was not intended to be part of the present invention.

Additionally, at Page 3 of the pending Final Official Action, the Examiner states that "Live cell vaccines to bacteria have been known in the prior art for some time". To the extent that this unsupported assertion is apparently part of the section 102 rejection, it should either be clarified or simply withdrawn. Applicant herein is claiming a method, not a composition, and there is believed to be no prior art that shows safe vaccination of avian eggs. Indeed, Thoma et al., as mentioned immediately above (and see all the related discussion below) clearly highlights the very safety issue for live cell vaccines, therefore the Examiner's assertion cannot support the section 102 rejection, nor a section 103 rejection.

The Section 103 rejections

In the Reply paper of July 16, 2009, Applicant carefully set forth that the present invention was novel, that it clearly did not exist in the references cited by the Examiner, and that the overall state of the art clearly taught against the usefulness of such an invention based on concerns for pathology to the avian embryos.

At page 6 of the pending Final Official Action, there is presented the often-repeated Office response that "In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references" and further bridging pages 6-7, the Official Action states "Additionally, the methods instantly claimed merely teach the use of

live cells of any Campylobacter species which was used in the prior art, whether this had some negative results to some of the eggs immunized and some positive results. There does not appear to be anything structurally different to the composition of the instant claims to allow for it to be safely administered. Accordingly, the method and the materials in the instant claims are identical to the that [sic] in ovo challenge using live cells which lead to persistently infected birds in Ziprin."

Applicant's overall comments to the gist of the Examiner's section 103 rejections are as follows. First, Applicant is not attacking references individually, Applicant is pointing out that there are, in fact, no credible teachings to combine. Additionally, it is the Examiner who is misapplying the references, because by picking and choosing specific passages from the references, and imputing to them a needed meaning, the entire overall teaching of the art [..that live cell vaccination is unsafe…] is being, in fact, ignored. And it is the overall state of the art against which nonobviousness must be judged.

. Second, Applicant has, in fact, correctly pointed out that Ziprin et al. is directed to colonization experiments, and persistent infection, which is not the same as whether or not any protective immune response has been achieved. "Inducing an immune response" as herein claimed is a specially defined term, provided at page 4, lines 33-37 of the present specification, and there is no demonstration or suggestion in Ziprin et al. that such a protective state has been achieved. Given that the persistently infected bird is harboring an organism that may in fact cause no harm whatsoever-- to the bird-- it is not clear that an immune response would *necessarily and reasonably* result, and Ziprin et al. does not so state. In effect, when the Examiner declares that Applicant's methods (Page 7 in the Official Action) are the same as the prior art, the result is actually to make a new rejection for inherency, which is not *reasonably and predictably* supported by the very references on which it is platformed.

The patentability of the present invention cannot be barred merely because the Applicant has discovered that those who came before were wrong, and the experimental section of the present application does more than 'use any Campylobacter used in the prior art' [see Page the Official Action bridging pages 6-7], rather, the Examples show that vaccination in ovo is effective, resulting in colonization and immune response.

Thus, in discussing the references that have been cited in support of rejections that have been made under 35 USC section 103, attention may first be directed to the previously cited article by G.C. Mead (World Poultry Science Journal, vol. 58, 2002, pp. 169-178), and

which reflects the thinking of those skilled in the art as of June 2002. The *Mead* article points to additional factors recognized in the art, that additionally teach away from the present invention. Not only are live bacterial vaccines generally known to be unsafe for administration to avian eggs (as the '408 patent clearly teaches), but *Campylobacter* species possess unusual growth and behavior characteristics.

Campylobacter are best characterized as microaerophiles that live in the mucosa of the intestine. As explained by Mead (see the Abstract, for example), *Campylobacter* rarely cause disease in poultry, and they are carried asymptomatically in the alimentary tract of affected birds. Successful colonization of the intestinal villi may also involve numerous other environmental factors, and host interactions, which are not well understood. There is, however, considerable evidence that *Campylobacter* infection in poultry can lead to human enteritis, and therefore preventing the spread of the bacterium in farm poultry is of great importance to human health. Although there are numerous approaches to providing bird flocks which are "Campylobacter-safe" (see Mead at 173) such as pre-colonizing the intestine with other competing bacterial species, there remains the clear problem that avian species are not to be *obviously* expected to mount vigorous immune responses against a microorganism that apparently causes them no harm., and even if an "immune response" is detected, is it of a kind that provides any practical effect and benefit. Further, if such immunization is to be accomplished, the question is how. As a result, it will be seen that there is no combination of the references cited under 35 USC section 103 that credibly predicts that the present invention would be successful.

The Examiner has rejected Claims 1-4, 6-8, and 13-15 under section 103 under a combination of *Noor et al.* and *Ziprin et al.* The rejection is respectfully traversed. Simply stated, there is nothing to combine, since, as the Examiner also notes, *Noor et al.* does not disclose live vaccines, and *Ziprin et al.* only discloses colonization experiments with live strains (including to elucidate the effects of mutations), with the intent of finding methods to prevent colonization, which is not obviously the same as causing and quantifying any effective immune that may, or may not be detected.

More specifically, *Ziprin et al.* is directed to the role of some *Campylobacter jenuni* genes on cecal colonization , and liver invasion. *Ziprin et al.* also discloses the in ovo delivery of certain *C. jejuni* strains, and strains containing mutations, to chicken embryos. The subsequent effect on cecal colonization and liver invasion in 14-day old in ovo-challenged birds was also measured. No information can be found in this reference that

teaches that in ovo delivery of a live strain of *Campylobacter* induces an immune response which provides some degree of protection against colonization. In fact, the reference teaches that the in ovo challenge route using live cells of Campylobacter can lead to persistently infected birds.

Again referring to Mead (see at Page 171, first full paragraph, line 3), "although infection is associated with the production of specific immunoglobin (Cawthraw et al. 1994), these appear to have little or no effect on levels of intestinal carriage or the susceptibility to infection." Therefore, it is difficult to imagine that those skilled in the art would have concluded or even expected that the in ovo route would induce an immune response to infection, that is ultimately medically beneficial to human consumers, by actually protecting against intestinal colonization by *Campylobacter* in poultry. At Page 8 of the pending Final Action, it is believed that the Mead et al. reference is being misapplied, since there was no disclosure in the reference that the resultant immunoglobin was in any way immunoprotective (page 171). Indeed, Example 6 of the present specification is the first proof that reasonable success is possible, in regard of protecting against *Campylobacter* via live *in ovo* delivery to such immunologically immature animals, avian embryos. The totality of the references does not therefore support a *prima facie* rejection, especially in regard of a large scale and dependable process which is safe for the immunized birds.

Applicant respectfully believes that it is not necessary to address the remaining rejections, which the Examiner will recognize are only directed to specific and straightforward features in certain dependent claims.

Conclusion

An RCE Transmittal and Petition for Extension of Time (five months) are both attached. The Patent Office is authorized to charge any needed fee, or fee deficiency, to Applicant's Deposit Account, No. 16-1445. An early and favorable action is respectfully requested.

Respectfully submitted,

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